Investigation on the Condensation of α and β Ketoaldehydes with Hydroxyaromatic Compounds

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Received July 24, 2004

Mechanism of the condensation reactions of methylglyoxal, phenylglyoxal and benzoylacetaldehyde with phenolic compounds have been discussed. It was observed that the reaction mechanisms changed depending on the type of the phenolic and also dicarbonyl compounds. While, methylglyoxal gave the angular methyl derivative of naphthofuraranonaphthofuran with 2-naphthol, phenylglyoxal and its *p*-chloro and *p*-methoxy derivatives formed benzo[*b*]naphtho[2,1-*f*]oxepine-13-ones. However, resorcinol behaved different and gave 2-phenyl-3-(2,4-dihydroxy)-6-hydroxy-benzo[*b*]furans with phenylglyoxal derivatives. 2-Phenyl-4-(2-hydroxynaphthyl)-4*H*-naphtho[*b*]pyran was produced from the reaction of benzoylacetaldehyde and 2-naphthol, but the reaction product was 3,9-dihydroxy-6-phenyl-6,12-methano-12*H*-dibenzo[1,3]dioxocin when the same carbonyl compound reacted with resorcinol.

J. Heterocyclic Chem., **41**, 205 (2004).

Introduction.

Condensation reactions of α,β,γ-dialdehydes with mono and dihydroxynaphthalenes have been carried out in the previous reports [1,2]. Condensation reactions of dihydroxynaphthalenes with dialdehydes were used for the formation of ladder type polymers [3]. When condensation reactions were run between glyoxal, malonaldehyde and glutaraldehyde with 2-naphthol, naphthofuranonaphthofuran, methano-dinaphtho-1,3- dioxocin and propano-dinaphtho-1,3- dioxocin derivatives were produced respectively (**I**, **II**, **III**). However, when 2-thionaphthol was used instead of 2-naphthol, similar products were isolated but the reaction

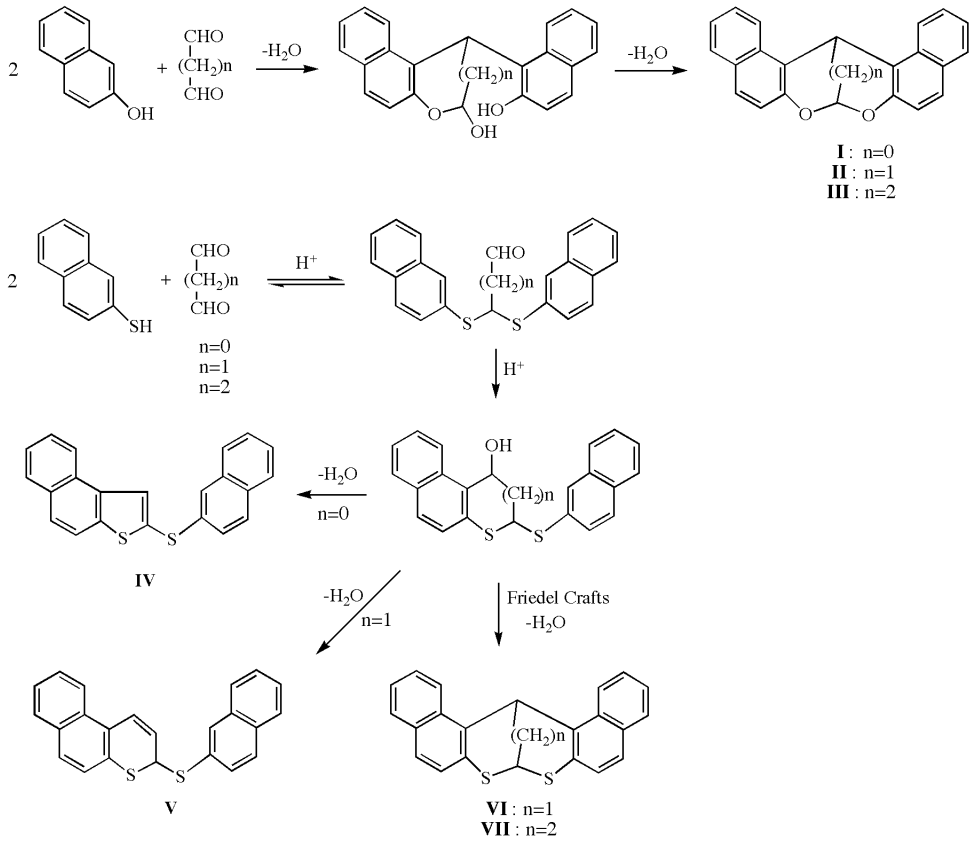
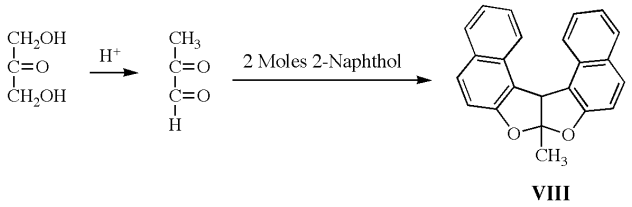


Figure 1

proceeded by a different mechanism. In the case of 2-naphthol, first Friedel-Crafts then intramolecular acetalisation reactions occurred, whereas 2-thionaphthol preferred first thioacetalisation reaction and gave naphthothiophen, naphthothiopyran, methanonaphthodithiocin and propanenaphthadithiocin type compounds with respect to the structure of the dialdehyde compounds (**IV**, **V**, **VI**, **VII**).

Results and Discussion.

As seen from previous reports, the reaction mechanism changed depending on the structure of the hydroxyaromatic compounds. In order to continue finding out the effect of the structure of the dicarbonyl compounds on the reaction mechanism, we worked with some 1,2-and 1,3-ketoaldehydes instead of dialdehydes. Methylglyoxal and phenylglyoxal were chosen as starting materials. Methylglyoxal has been formed *in situ* from dihydroxyacetone by Mattox rearrangement [4] in order to avoid the water solution of methylglyoxal. The product was the angular methyl derivative of napthofuranonaphthofuran (**VIII**) (Figure 2). Reaction proceeded by the reaction mechanism defined previously [1,2].

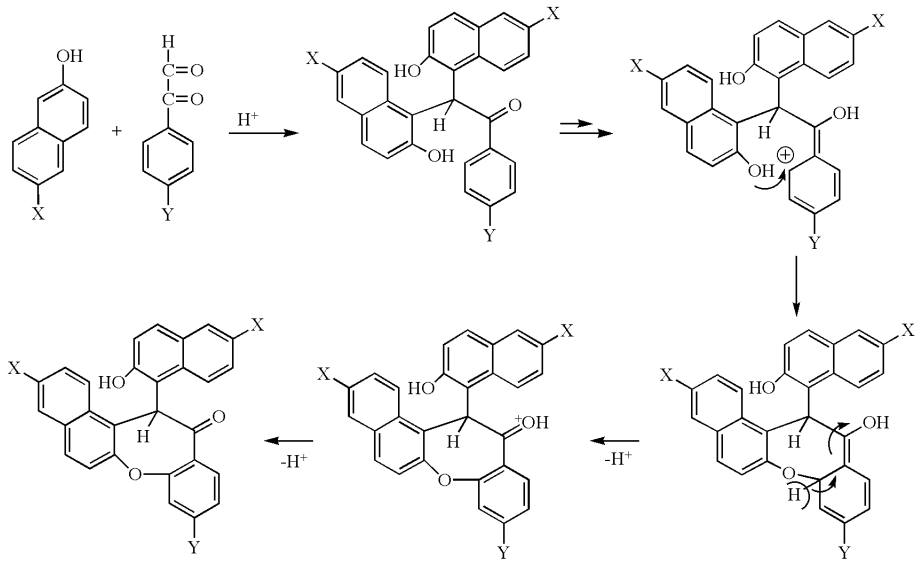


VIII

Figure 2

However, phenylglyoxal gave a completely different product, the benzo[*b*]naphtho[1,2-*f*]oxepine-13-one derivative (**IXa**), unexpectedly. Probable reaction mechanism for the formation of this new compound was illustrated below (Figure 3). The initial step involving the protonation of the aldehyde carbonyl group was followed by the condensation with two moles of 2-naphthols as it is for dialdehydes. The acid catalyst protonated the oxygen of the carbonyl group of the intermediate and increased the electrophilicity of the *ortho* position of the aromatic ring. Therefore, the hydroxyl group of the 2-naphthol attacked to the *ortho* position of the phenyl ring. Then the ring lost a proton and gained aromatic character. While the attack on the ring was nucleophilic, the leaving group was an electrophile, a proton. This step is analogues to the last step of the Bamberger Rearrangement [5].

The structure of the product has been solved on the basis of its spectral data. The IR spectrum shows signals corresponding to hydroxyl and carbonyl functional groups. Mass spectrometry provided further evidence for the proposed structure and major peaks could be explained in terms of fragmentation [6] (Figure 4). By high resolution mass spectrometry and elemental analysis the molecular composition was established as $C_{28}H_{18}O_3$ (M^+ 402). The principal ions were observed at m/z 259, 231,171,105.



IX a : X : H, Y : H
b : X : Br, Y : H
c : X : H, Y : OCH_3
d : X : H, Y : Cl

Figure 3

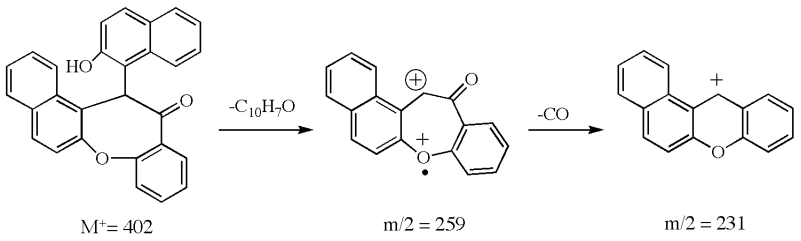


Figure 4

One of the evidences for this mechanism is the observed increase in the yield as electron withdrawing groups are attached to the phenyl ring. The formation mechanism of these unexpected compounds was interesting. This method may be an alternative method, since dibenz[*bf*]oxepine-10-one systems have been synthesized until now mainly starting from phenoxyphenyl acetic acid [7-10].

Further studies were performed between phenylglyoxal and resorcinol. It is interesting to note that resorcinol gave completely different products (benzofuran derivative) *via* a Friedel-Crafts reaction followed by semiacetalisation and also water elimination reactions (Figure 5). After the initial Friedel-Crafts reaction, intermediate could give the semiacetalisation reaction. This step was prevented by the steric bulk and low nucleophilicity of the naphthol ring.

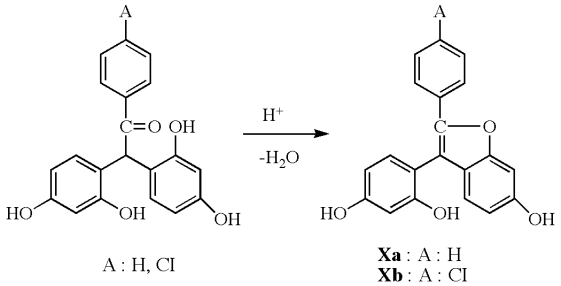


Figure 5

To reinforce the steric and electronic effects of 2-naphthol and resorcinol on the reaction mechanism, a β-ketoaldehyde, benzoylacetaldehyde, was treated with two compounds. 2-Naphthol gave product (**XI**) which formed by Friedel-Crafts and semiacetalisation followed by water elimination reactions. ^{1}H-NMR of the (**XI**) had only one singlet for hydroxyl group at about 9 ppm. The benzylic and olefinic protons could not split each other because of the 90° dihedral angle and they were seen as two singlets at 4.7 and 4.8 ppm. In the case of resorcinol, the reaction proceeded by a similar pathway however, after the initial step, intramolecular acetalisation occurred as reported earlier [1,2]. In these reactions, final nucleophilic attack was toward the carbonyl group not the phenyl ring as in that of phenylglyoxal.

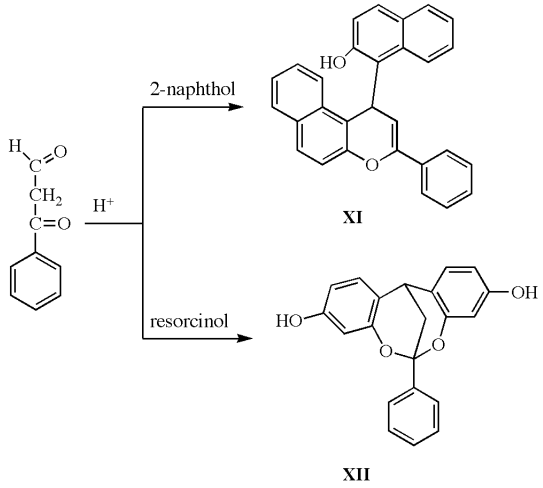


Figure 6

In conclusion, the reactions went through different pathways depending on the type of carbonyl and phenolic compounds involved. Whereas methylglyoxal formed acetalic product, 7a-methyl-7a,14c-dihydronaphthofuro[2,1-*b*]-naphtho[1'2';4,5]furo[3,2-*d*]furan (**VIII**) with 2-naphthol, phenylglyoxal and derivatives behaved different and gave etheric products 12-(2-hydroxy-1-naphthyl)-benzo[*b*]-naphtho[2,1-*f*]oxepine-13-ones (**IX a-d**). 2-Naphthol could not form acetalic or semiacetalic product with phenylglyoxal because of the steric and electronic effects of the phenyl ring. However, the smaller and more powerful nucleophile resorcinol could produce semiacetalic products**,** 2-phenyl-3-(2,4-dihydroxyphenyl)-6-hydroxy-benzo[*b*]furans (**Xa-b**), but not acetalic compounds because of the steric effect of the phenyl group.

In the case of benzoylacetaldehyde, the smaller nucleophile resorcinol could give an acetalic product, 3,9-dihydroxy-6-phenyl-6,12-methano-12*H*-dibenz[*d,g*][1,3]dioxocin (**XII**). Since the formation of this type of compound was prevented by the bulky nucleophile, 2-naphthol could only give a semiacetalic product, 2-phenyl-4-(2-hydroxy-naphthyl)-4*H*-naphtho[*b*]pyran (**XI**).

EXPERIMENTAL

General.

IR spectra have been run on a FT-IR 5300 spectrophotometer. NMR spectra were measured on a 250 MHz Brucker instrument using TMS as an internal reference. Mass spectra were obtained using a DS-55 model instrument and elemental analyses were carried out at the University of East Anglia, England. Phenylglyoxal monohydrate and derivatives were prepared by literature method [11].

Synthesis of 7a-Methyl-7a,14c-dihydronaphthofuro[2,1-*b*]naphtho[1'2';4,5]furo[3,2-*d*]furan (**VIII**).

Dihydroxyacetone (9 g, 100 mmol) and 2-naphthol (28.8 g, 200 mmol) were reacted in 50 ml alcohol using (0.6 ml, 10 mmol) phosphoric acid 85 % as catalyst for 8 h at 80 °C. The mixture was neutralized with Na_2CO_3 and the precipitated salt was filtered off. Alcohol was evaporated to the approximately 20 ml and solution was kept –5 °C for 12 h. Precipitated crystals were collected by filtration and recrystallized from acetone/water (3/1) mixture as white needles to yield (16.2 g, 50%). Mp 220-221 °C IR (KBr disc): ν 3100, 2950, 1620, 1580, 1360, 1250 (O-C-O), 1150; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.93 (s, 3H, methyl), 5.26 (s, 1H, 14Hc), 8.30 (d, 2H, *J*=8.4 Hz, 1 and 14H), 7.81 (d, 2H, *J*=8.1Hz, 4 and11H), 7.65 (d, 2H, *J*=8.8 Hz, 5 and 10H), 7.51 (t, 2H, *J*=8.4Hz, *J*=1.2 Hz, 2 and 13H), 7.35 (t, 2H, *J*=8.1 *J*=1.1 Hz, 3 and 12 H), 7.2 (d, 2H, *J*= 8.8 Hz, 6 and 9H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 22.2 (CH_3), 53.2 (14c), 112.4, 119.2, 123.1, 123.6, 124.5, 126.2, 126.9, 130.5, 130.1, 156.3; MS *m/z* (%) 324 (100), 281(35), 252(30), 162(10), 126(15), 79(20).

Anal. Calcd. for $C_{23}H_{16}O_2$: C 85.03; H 4.93. Found: C 85.41; H 4.87.

General Procedure for the Synthesis of **IXa**, **IXb**, **IXc**, **Ixd**.

Arylglyoxal (100 mmol) and phenolic compound (200 mmol) were reacted in acetic acid using sulphuric acid (10 mmol) as catalyst for 12 h at 50 °C. Then the mixture was poured into water, precipitate was collected by filteration and washed with alcohol to remove the unreacted phenolic compounds, then crystallized from pyridine.

12-(2-Hydroxy-1-naphthyl)-benzo[*b*]naphtho[2,1-*f*]oxepine-13-one (**IXa**).

This compound was obtained as white needles to yield (16.6 g, 40%), Mp 292-293 °C. IR (KBr disc): ν 3400, 3050, 1700, 1620, 1580, 1450, 1260, 1180; ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.3 (s, 1H, OH), 8.6-7.1 (m,17H); ^{13}C NMR (250 MHz, $CDCl_3$): δ 195.7 (C=O) 173.4 (O-CH) 139.7, 132.1, 131.5, 130.7, 129.9, 129.5, 129.3, 129.2, 128.8, 128.4, 128.2, 127.8, 127.6, 127.3, 125.4, 123.2, 113.5, 110.2, 90.9; MS *m/z* (%) 402(30), 259, 231(45), 202(20), 171(50), 105(70), 31(100).

Anal. Calcd. for $C_{28}H_{18}O_3$: C 83.5; H 4.47. Found: C 83.8; H 4.42.

12-(2-Hydroxy-6-Bromo-1-naphthyl)-benzo[*b*]naphtho[2,1-*f*]-oxepine-13-one (**IXb**).

This compound was obtained as white needles to yield (16.8 g, 35%). Mp 287-288 °C. IR (KBr disc): ν 3450, 3150, 2860, 1700, 1630, 1580, 1520, 1270, 1190, 1020; ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.3 (s, 1H, OH), 8.6-7.1 (m, 15H); MS *m/z* (%) 560 (3), 337(2), 278(25), 207(45), 140(25), 105 (50), 77(100).

Anal. Calcd.for $C_{28}H_{16}O_3Br$: C 60.02; H 2.85. Found: C 61.01; H 2.91.

12-(2-Hydroxy-1-naphthyl)-4-methoxy-benzo[*b*]naphtho[2,1-*f*]-oxepine-13-one (**IXc**).

This compound was obtained as white needles to yield (17.36 g 40%). Mp 304-306 °C. IR (KBr disc): ν 3452, 3067, 2935, 2839, 1699, 1631, 1579, 1510, 1460, 1253. ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.1 (s, 1H, OH), 8.7-6.8 (m, 17H), 3.13 (s, 3H, CH_3); MS *m/z* (%) 432(5), 290(92), 261(100), 247(66), 231(85), 218(45), 189(50), 126(80), 77(35).

Anal. Calcd. for $C_{29}H_{20}O_4$: C 80.5; H 4.62. Found: C 81.1; H 5.01.

12-(2-Hydroxy-1-naphthyl)-4-chloro-benzo[*b*]naphtho[2,1-*f*]-oxepine-13-one (**IXd**).

This compound was obtained as white needles to yield (26.31 g, 60%). Mp 306-309°C. IR (KBr disc): ν 3400, 1700, 1630, 1580, 1510, 1456, 1260, 1020, 830, 740; ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.05 (s, 1H, OH), 8.8-6.9 (m, 15H); MS *m/z* (%) 436(2), 310(6), 294(100), 265(26), 253(24), 231(38), 202(22), 154(30), 144(43), 126(50), 115(20), 104(27), 76(23).

Anal. Calcd. for $C_{28}H_{16}O_3Cl$: C 77.06; H 3.62. Found: C 77.41; H 3.12

General Procedure for the Synthesis of **Xa**, **Xb**, **XI** and **XII**.

100 mmol of Hydroxy aromatic compound and 50 mmol carbonyl compound were dissolved in toluene and then 5 mmol *p*-toluene sulphonic acid was added and the mixture was heated to 70-80 °C for 12 h. At the end of the reaction, toluene was removed by vacuum distillation. The residue was heated with water to remove the unreacted phenolic compound. Then the undissolved material was collected by filtration and crystallized from the appropriate solvent.

2-Phenyl-3-(2,4-dihydroxyphenyl)-6-hydroxy-benzo[*b*]furan (**Xa**).

This compound was obtained as white needles (dichloromethane) to yield (1.908 g, 60 %). Mp. 190-193 °C. IR (KBr): ν 3400, 2920, 1620, 1600, 1115; ^{1}H NMR (250 MHz, $DMSOd_6$): δ 9.45 (s, 1H, OH), 9.21 (s, 1H, OH), 9.13 (s, 1H, OH), 7.6 (dd, *J*=8.4 Hz, *J*=1.4 Hz, 2H ar), 7.3-7.2 (m, 3H ar), 7.0 (t, *J*=8.4 Hz, *J*=1.3 Hz, 2H, ar), 6.9 (d, *J*=2.3 Hz, 1H, ar), 6.7 (dd, *J*=8.2 Hz, *J*=2.1 Hz, 1H, ar), 6.4 (d, *J*=2.1 Hz, 1H ar), 6.25 (dd, *J*=8.2 Hz, *J*=2.1 Hz, 1H ar); MS *m/z* (%) 319(M+1,100), 318 (56), 289(45), 273(35), 261(18), 247(35), 243(25), 213(45), 189(28), 159(40), 105(35), 77(45).

Anal. Calcd. for $C_{20}H_{14}O_4$: C 75.47; H 4.40. Found: C 75.05; H 4.06.

2-(4-Chlorophenyl)-3-(2,4-dihydroxyphenyl)-6-hydroxy-benzo-[*b*]furan (**Xb**).

This compound was obtained as white needles (toluene) to yield (1.83 g, 52 %). Mp.270-272 °C. IR (KBr) ν 3300, 1621, 1610, 1480, 1100, 980; ^{1}H NMR (250 MHz, $DMSOd_6$): δ 9.4 (s, 1H, OH), 9.33 (s, 1H, OH), 9.18 (s, 1H, OH), 7.5 (dd, *J*=8.2 Hz, *J*=1.6, 2H ar), 7.2 (d, *J*=8.1 Hz, 2H ar), 6.9 (d, *J*=8.0 Hz, 1H ar), 6.7 (dd, *J*=8.1 Hz, *J*=2.0 Hz, 2H ar), 6.5 (d, *J*=2.1 Hz, 1H, ar), 6.33 (d, *J*=2.0 Hz, 1H ar), 6.28 (d, *J*=1.0 Hz, 1H ar); MS *m/z* (%) 352(100), 323(15), 316(20), 289(15), 271(16), 247(15), 213(25), 158.5(22), 135.5(26), 111(10).

Anal. Calcd. for $C_{20}H_{13}O_4Cl$: C 68.18; H 3.69. Found: C 68.57; H 3.71.

2-Phenyl-4-(2-hydroxynaphthyl)-4*H*-naphtho[*b*]pyran (**XI**).

This compound was obtained as white needles (petroleum ether) to yield (1.92 g, 48 %). Mp. 113-117°C. IR (KBr) ν 3400, 1620, 1600, 1510, 1480, 1150. ^{1}H NMR (250 MHz, $DMSOd_6$): δ 9.3 (s, 1H, OH), 8.1-7.1 (m, 17H, ar), 4.82 (s,1H, olefinic), 4.7 s, 1H benzylic); MS *m/z* (%) 400(10), 310(20), 281(55), 253(100), 180(12), 163(52), 149(62), 104(87), 78(86).

Anal. Calcd for $C_{29}H_{20}O_2$: C 87.0; H 5.0. Found: C 87.31; H 4.95.

3,9-Dihydroxy-6-phenyl-6,12-methano-12*H*-dibenz[*d*,*g*][1,3]-dioxocin (**XII**).

This compound was obtained as white needles (dichloromethane) to yield (1.99 g, 60 %). Mp 278-279 °C. IR (KBr) ν 3300, 1630, 1520, 1480, 1260, 1150, 1050, 980; ^{1}H NMR (250 MHz, $DMSOd_6$): δ 9.35 (s, 2H, OH), 7.8 (dd, *J*=8.9, *J*=2.1, 2H, ar), 7.5 (d, *J*=9.0, 2H, ar), 6.3 (m, 5H, phenyl), 4.0 (t, 1H benzylic), 2.8 (d, *J*=2.8 Hz, 2H, CH_2); MS *m/z* (%) 332(100), 315(40), 255(78), 241(20), 223(98), 210(77), 165(32), 152(18), 105(17), 77(46).

Anal. Calcd for $C_{21}H_{16}O_4$: C 75.9; H 4.82. Found: C 75.5; H 4.48.

Preparation of Benzoylacetaldehyde.

Dispersion of sodium hydride in parafin (60%) (6 g, 25 mmol) was put into a round bottom flask and washed 2-3 times with ether. Then dried ether (100 ml) and methanol (10 ml, 25 mmol) were added. After the gas evolution stopped, the mixture was heated. After cooling to –5 °C, ethylformate (18.5 g, 25 mmol) and 160 ml ether were added slowly keeping the temperature at 5 °C. After addition, the reaction was continued at room temperature for 3 h. The formed sodium salt of benzoylacetaldehyde was collected by filtration, washed with ether and dried in a vacuum oven. Before using, it was converted to the benzoylacetaldeyde with acetic acid and reacted with phenolic compounds immediately.

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